THE PATHOLOGICAL ANATOMY OF "A FATAL DISEASE OF INFANCY, WITH SYMMETRICAL CHANGES IN THE REGION OF THE YELLOW SPOT" (WARREN TAY), "AMAUROTIC FAMILY IDIOCY" (SACHS), "INFANTILE CEREBRAL DEGENERATION" (KINGDON AND RUSSELL).[1]

By WILLIAM HIRSCH, M. D.

The first case of this peculiar disease has been described in the year 1881 by Waren Tay, under the name of "Symmetrical Changes in the Region of the Yellow Spot in Each Eye of an Infant." Since that time a number of other cases have been brought to light by different observers, so that the total list up to to-day amounts to 26 cases, including my own. For quite a number of years after Tay's first publication, various observers paid almost exclusive attention to one particular symptom of the disease—that is, to the peculiar ophthalmoscopical condition. Only after some time was it realized that we had to deal, not with a localized affection of the eye, but with a more extensive disease of the central nervous system. The credit for having first called the neurologists' attention to this peculiar affection belongs to B. Sachs. The clinical symptoms have ever since been so accurately described that nothing new can be added in this respect for the present. The main features of the disease, which are almost absolutely uniform in all cases, are the following:

The parents of these children are strong and healthy, and give no history of syphilis or tuberculosis. They all belong to the same race; they are, with few exceptions, eastern Jews. There are always several children of the same mother affected. In some cases there are healthy children between the affected ones; in others, all the children in the family are affected in the same way. The sex seems not to have any influence on the disease. The children are born apparently in good health and develop normally up to the third or fifth month of age. Between the third and eighth month the muscles begin to become flabby and weak. The child is no longer able to sit up or to hold up its head. The reflexes remain present, as a rule. In some cases the extremities become rigid and contracted; mental development is arrested; the children become dull and apathetic; the eyesight gradually diminishes to complete blindness. In most cases there is a marked hyperacuity, and some children are hypersensitive to touch. The most characteristic symptom, which, in fact, gave rise to the discovery of the disease, is the peculiar changes on the retina. The assumption of some observers, that these changes are congenital, is apparently erroneous. When the peculiar ophthalmoscopical picture has developed, we find in the region of the yellow spot a whitish opacity, the centre of which shows a cherry-red spot. The discs appear at first normal, but undergo atrophy later on. The following is the history of my own case:

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[1] The figures accompanying this paper are photographs from diagrams made for a demonstration at the twenty-fourth annual meeting of the American Neurological Association, on which occasion this paper was read.

L. P., son of healthy parents of the eastern Jewish race, was brought to my clinic in July, 1896. The child, which was then ten months old, had developed well until the age of six months, when it began to be weak in the back, so that it lost the ability to sit up. The mother stated that she had lost two other children at the age of eighteen and twenty months, respectively, which apparently presented the same condition as the patient. The muscles of the whole body were very flabby, and the child was unable to hold up its head or to sit without support. It had normal perception of light, and there was marked hyperacuity—a symptom which the mother had also observed in the two other children. The reflexes were present; sensation was normal; the internal organs were also in a normal condition. The ophthalmoscopical examination revealed the typical picture described above. The child continued to become gradually weaker, until it died, on the 27th of July, 1897, twenty-two months old. An autopsy was made four hours after death.

So far five autopsies have been performed—two by Sachs and three by Kingdon and Russell. In the first case of Sachs, only the cortex of the brain was examined; in the second case, sections were made through all parts of the cortex, of the ganglia, of the optic chiasm, of the pons, the medulla and the cervical cord. The result of the examination of these two cases was alike. There was an equal change of the pyramidal cells throughout the whole cortex of the brain. The contours of the cells were rounded, and the cells exhibited every possible change of their protoplasmodic substance. In the neuroglia there were no evident changes, nor was there any distinct sclerosis in any part of the brain. The blood vessels were found perfectly normal in every respect. The spinal cord, it was said, contained no changes in the gray matter, but exhibited a degeneration of the lateral areas, including the pyramidal tracts, and extending to the periphery. From these findings the conclusion was drawn that the disease was confined to the cells of the cortex of the brain, and consisted of an arrested development of this organ.

Quite in accordance with this view was the result of the three autopsies of Kingdon and Russell. They found the same changes in the pyramidal cells of the cortex, and state expressively that the basal ganglia, the cerebellum, the cells of the posterior column nuclei, and the gray matter of the spinal cord exhibited no changes whatsoever. In the lateral tracts they found the same degeneration which had been described by Sachs.

On the strength of these findings these authors also were led to believe that the disease was limited to the cortex of the cerebrum. They did not, however, agree with Sachs in the assumption of an arrested development, but considered the condition a degenerative process. The nature of this process was left an open question.

In accordance with their respective views, Sachs published his first cases under the title of "Arrested Cerebral Development" and "Agenesis Corticalis," while Kingdon and Russell called the disease "Infantile Cerebral Degeneration." Recognizing the insufficient anatomical base on which the disease stood at that time, Sachs preferred a clinical designation, and proposed the name of "Amaurotic Family Idiocy."

I will now refer to the result of the post-mortem examination of my own case, which I hope will throw some light on the different questions:

As stated before, the autopsy was made four hours after death. The skull was thick and symmetrical, and both fontanelles were closed. The dura was adherent to the skull. The pia could easily be removed from the brain. The macroscopical inspection of the brain showed no abnormal conditions. There was no œdema of the convexity, and no increase of fluid in the lateral ventricles. There were no abnormalities of fissuration, except an unusual prolongation of the second temporal fissure. The entire brain, with the medulla oblongata and the spinal cord, was put immediately after the removal in a 10 per cent. formaline solution. Both the eyes were removed, and one put in formaline and the other in Müller's fluid. After the hardening process the whole central nervous system was cut into small pieces and imbedded in paraffine. Serial sections, varying in thickness from one to four microns, were made through the whole spinal cord, the medulla oblongata, corpora quadrigemina, optic thalamus, nucleus caudatus, chiasm, optic nerves, and through the entire cortex of the cerebrum and cerebellum. The sections were stained with various aniline dyes, as methylene blue, eosin, thionin, nigrosin, fuchsin and with different kinds of hæmatoxylin.

For practical reasons I will begin the description of the different sections with that of the spinal cord. I found the same degeneration of the pyramidal tracts which had been described by the other observers. But, in addition to this, there are very pronounced changes throughout the entire gray matter of the cord. All the nerve cells of the anterior, as well as of the posterior, horns are enormously enlarged. They appear blown up and round in shape. The nucleus is well defined, and invariably moved toward the periphery of the cell body. It contains a nucleolus which is stained dark and has a sharp outline. The cell body is surrounded by a membrane. On account of the enormous enlargement, the cells appear much more numerous than normally, so that some parts of the gray matter seem to consist almost exclusively of cells. The most peculiar aspect is offered by the motor cells of the anterior horns. (Fig. I.) They are more than twice their normal size. Many of them appear as round masses, without any nucleus. This, however, can be shown by serial sections to be due to the direction of the cut through the cell. In fact, all the motor cells contain a nucleus and nucleolus. Some of the cell bodies are vacuolated, the vacuoles being lined with a membrane. The processes of the cells, the dendrites, as well as the axis cylinder, seem to be very few, and often they appear to be broken off the cell. In most instances the cells are immediately surrounded by connective tissue, the pericellular space being small or missing altogether. The nucleus, which is invariably situated near the periphery of the cell body, is surrounded by a dark zone, which gradually shades off into a more or less colorless area. When we come to study the minute structure of these cells with a high power, we find that the Nissl bodies have disappeared entirely. The dark zone around the nucleus consists of a granular mass, which is probably formed by broken-up Nissl bodies, which appear to be in a condition of pulverization. The light area of the cell body is made up of a very fine network. In a very few instances the dark zone around the nucleus contains a few normal chromatic bodies.

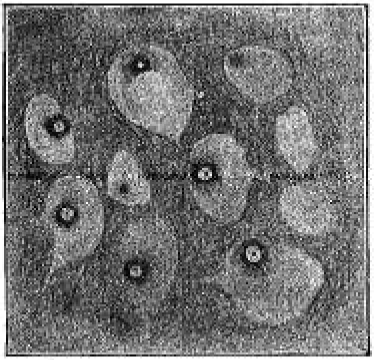

FIG. I.

Cross-section through the anterior horn of the cervical part of the spinal cord.

The cells of the posterior horns (Fig. II.) are also changed in the same manner. They, too, through their enormous enlargement, appear very numerous, and wherever the section has occurred, above or below the nucleus, the cell looks like a big, round mass, without any definite structure. As we approach the medulla oblongata, we find the same changes in all the nerve cells; not only all the nuclei of the cranial nerves, from the hypoglossus to the oculomotorius, but also the cells of the reticulum, the olivary bodies, the pons, are all changed

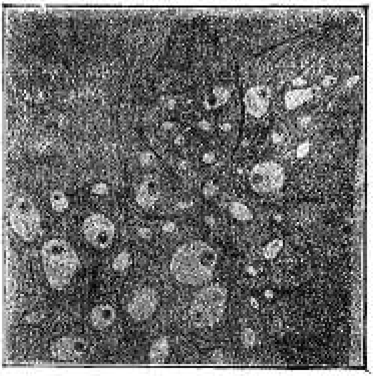

Fig. II.

Cross-section through the posterior horn of the cervical part of the spinal cord.

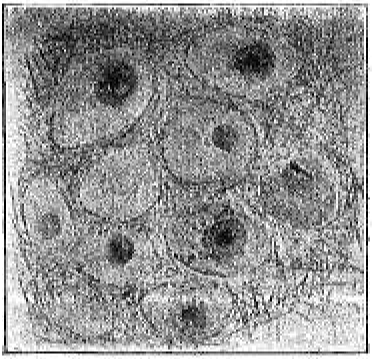

Fig. III.

Cross-section through the motor nucleus of the trigeminal nerve.

in the same typical manner. According to the conditions of their natural shape, they appear also different in their morbid condition. The cells of the olivary bodies are round in shape, showing a sharply defined nucleus and nucleolus. The cells of the reticulum and the pons appear as oval-shaped bodies, and, owing to the fact that the nucleus is pushed to the periphery of the cell body, a great many cells are cut so that the nucleus does not appear in the section.

There are some groups of cells which seem to have undergone still further changes of decomposition. Such groups are principally found among the nuclei of the cranial nerves. The motor nucleus of the trigeminal nerve, for instance, contains cells which exhibit this condition. (Fig. III.) The nucleus has lost its sharp outline, and the nucleolus can hardly be recognized at all. The cell body is filled by irregular masses—apparently detritus of the normal protoplasm. Such masses of detritus are especially accumulated at the periphery of the cell body, and also in the pericellular lymph space. Cells of other groups, as, for instance, in the nucleus ambiguus, are remarkable for their peculiar elongated shape. (Fig. IV.) The dark zone around the nucleus shows distinct traces of the Nissl bodies, and the rest of the cell body, as in the cells of the anterior horns, is made up of a fine network. The nucleus appears as a homogeneous body, and the darkly stained nucleolus contains a light spot in its centre. The cells of the subcortical ganglia, the optic thalamus, the nucleus caudatus and the corpora quadrigemina exhibit exactly the same condition as the other cells. The cells of the substantia nigra show the

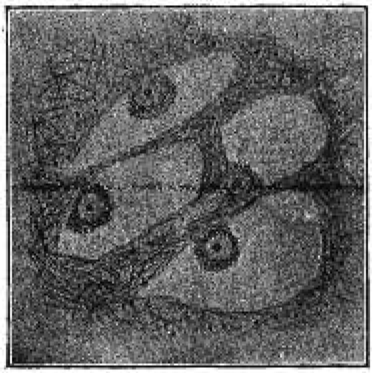

FIG. IV.

Cross-section through the nucleus ambiguus.

pigment very plainly, and otherwise exhibit the same changes of the nucleus and cell body.

The cortex itself, which was examined throughout the entire brain, shows the same typical changes all over. (Fig. V.) The different layers of the pyramidal cells can still be well differentiated; the cells themselves, however, are changed in the same typical manner. They are all considerably swollen, so that at some regions hardly anything but cells is to be seen. The nucleus is displaced to the periphery of the cell body, and in some instances projects considerably beyond the surface. The cells are nearly all of oval shape, and there is not a single cell in all the specimens which has retained its pyramidal character.

Comparatively small changes are found in the cerebellum.

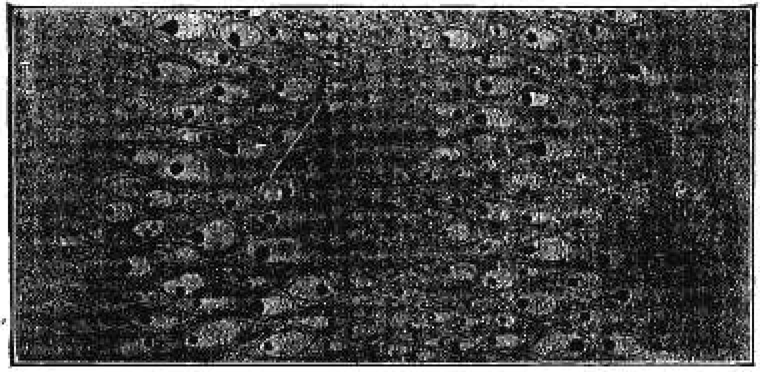

Fig. V.

Cross section through the cortex of the first frontal convolution.

The granular area shows no abnormal condition at all, while the Purkinje cells appear to be affected in some way, showing a much less distinct structure than under normal conditions, without, however, exhibiting the enlargement of the circumference of the cell body that was observed in all the other nerve cells of the nervous system.

The cross sections through the optic tract and the chiasm showed complete degeneration. The cauda equina was found to be perfectly normal, and so were all the roots of the spinal cord.

The eyes have been kindly examined by Dr. Holden, whose detailed report follows this paper.

The ganglion cells of the vesicular layer of the retina have been found in the same swollen condition as the cells of the central nervous system, and it is due to this condition of the cells that we find the peculiar ophthalmoscopical picture in this disease. As is well known, the only part of the retina in which the vesicular layer consists of more than one single layer of ganglion cells is the macula lutea. Here we have an accumulation of from six to seven layers of cells, and it is easily understood that when these cells become enormously enlarged, and their bodies offer an opaque character during life, they will produce the peculiar whitish opacity in the region of the macula.

So, then, we have an equal affection of all the nerve cells of the entire nervous system, the main features of which are a condition of chromatolysis and other degenerative processes of the protoplasm, combined with considerable swelling of the cell body and displacement of the nucleus toward the periphery of the cell. The neuroglia has been found to be perfectly normal, and no affection of the blood vessels could be noticed through the entire system.

There seems to be a discrepancy between these findings and those of the previous observers, the latter claiming only an affection of the cerebral cortex. This, however, seems to be due to the differences of the hardening process. Sachs, as well as Kingdon and Russell, has hardened the brain and cord in Müller's fluid, which does not permit of the study of the minute structure of the cells. Especially, changes in the smaller cells, as those of the posterior horns of the cord and the medulla oblongata, cannot be recognized in specimens hardened in Müller's fluid. That, in fact, Sachs' second case—in his first case only the cortex had been examined—offered the same change of the motor cells in the anterior horns of the cord as in my case, can easily be recognized from his specimens even to-day. Dr. Sachs was kind enough to put some of his specimens at my disposal, and when we came to compare them with my own, it was evident that we had to deal with perfectly analogous conditions. Although the Müller's fluid specimens do not show the peculiar structure of the cells, they show, however, sufficiently well the enlargement of the circumference of their bodies in the anterior and posterior horns, which could easily be overlooked, since changes in the structure of the cells necessarily escape observation. Inasmuch as the positive findings of Kingdon and Russell, whose cases were also hardened in Müller's fluid, are in perfect harmony with those of Sachs and myself, I do not hesitate to assume that their negative statement also could be modified in the same way as Sachs', and that the morbid changes in their cases, too, were not confined merely to the cortex of the brain.

So, it seems, then, to be an established fact that we have to deal not, as it was supposed, with an isolated cortical lesion, but with an affection of the entire nervous system. The next question to be decided would be: Of what nature is this affection? Have we to deal, as Sachs claims, with an arrested development, or, as Kingdon and Russell maintain, with a degenerative process—that is, an acquired disease?

Against the theory of an arrest of development stand both the clinical and anatomical facts. It is generally stated that these children are born in good health and well developed. In my own case the intelligent mother, who had previously lost two children of the same disease, watched the baby with the greatest anxiety, and still could not detect any morbid sign before the age of six months. Of great importance for the proper judgment of the nature of the disease is the fact that the peculiar ophthalmoscopical picture develops only comparatively late, sometimes long after the other symptoms have made their appearance. Since we know now that the peculiar condition of the macula lutea is due to a certain change of the ganglion cell layer, we are justified in assuming that the cells have been normal before the appearance of this peculiar picture. Besides this, there is no analogue in the whole embryology to this special affection of the nerve cells, nor could any arrest of development account for an affection of all the nerve cells, and nothing but the nerve cells, of the entire system.

If, then, we have to deal with an acquired disease, of what nature and of what origin could such disease be? The total absence of any affection of the blood vessels, as it could be stated in my case, as well as in the other cases, justifies us in excluding any inflammatory process. Primary idiopathic diseases of the nerve cells occur only as systemic diseases; but no disease is known in which simultaneously all the nerve cells of the entire system become diseased. Besides, in systemic diseases the anatomical picture of the cells is quite different from what we have found here. There we have the typical picture of atrophy of the cell, while here we have an anatomical condition which does not correspond to any of the idiopathic cell affections at all.

The only theory, then, which is left, and which in fact corresponds in every respect to the clinical and anatomical aspect of these cases, is to assume a toxic condition; to assume the action of a poison on the nerve cells. That poisons are really apt to act that way is a well-established fact. The anatomical picture of these cells also corresponds in every respect to those found after experimental poisoning. The chromatolysis, the swelling of the body, the displacement of the nucleus, the destruction and breaking off of the dendrites and the axis cylinder; all these are well known features of poisoning, and, in point of fact, symptoms unknown in any other condition. We have to distinguish between two different ways in which a poison might affect the nerve cells. It might either act directly on the cells, or it might produce a disturbance in the nutrition, and so, by changing their metabolism, cause a degeneration of the protoplasm. The total absence of any morbid changes in the blood vessels or in the neuroglia, the fact that the pathological changes are confined to the nerve cells exclusively, lead me to believe that the virus, whatever it may be, exerts a direct action on these cells, an assumption which I think finds further support in the anatomical appearance of the cells themselves.

The next question, then, would be: Of what nature is this poison, and where does it come from? This question cannot be answered yet with any amount of certainty. It would, of course, seem very tempting to assume a toxic condition of the mother's milk, as this would also easily explain the family type of the disease. But there are other possibilities to be considered, and so this question must be left open for further investigation. So much, however, I think can be said with certainty to-day—that this peculiar affection does not consist of an arrest of development, but is an acquired disease affecting the nerve cells of the entire system, produced by some poison. I would suggest that as soon as the diagnosis of such a case has been made, the child be taken from its mother's breast, and all future children be fed with other nourishment. Future investigations will have to be directed toward the clinical examination of the blood, and the excretions of these children, and of the milk of the mother, and it may be hoped that by these means all questions as to the nature and etiology of this interesting disease may be definitely determined.

166. KYSTES DU CERVEAU (Cerebral Cysts.) Jaboulay, (Lyon Médical, vol. 87, Jan. 23d, 1898).

This is a brief report of operation on eight non-parasitic cysts of the brain by an author who is very active in cerebral surgery. Most of the patients were epileptic, and the majority of the cysts were secondary formations following cranial injury. By far the best result obtained was in the case of a young man who, a year before, had sustained a fracture of the skull, for which a trepanation was done. He developed epilepsy, and in the cicatricial tissue a cyst was found and emptied. It is noted that after the operation "the seizures disappeared almost completely." Of the remaining seven cases, the patients either succumbed to the operation, were entirely unrelieved or showed a "slight amelioration," with the exception of the last, who had been operated upon only a month before, and who seemed decidedly improved. On the whole, the report shows again the fruitless results of indiscriminate operations on the brain. PATRICK.